REMARKS

Claims 31-41 and 46-61 were pending in this application. Claims 31, 32, 37, 38, 40 and 57 are currently amended without any intent of disclaiming equivalents thereof. New claim 62 is added. Accordingly, upon entry of this paper, claims 31-41 and 46-62 are pending and presented for consideration.

Claim Amendments

Independent claim 31 is amended to specifically recite "detecting a binding activity of von-Willebrand factor (vWF) in a sample to a soluble form or a portion of glycoprotein 1b(α) (GPlb(α)) that is not associated with a platelet in the presence of ristocetin or a functionally equivalent substance." Support for the amendment can be found in the specification at least, for example, on page 3, lines 1-3, page 5, lines 20-26, page 6, lines 23-24, and Example 3. Claim 31 is also amended to replace "a range of ratios established as normal range" with "a reference range." Support for the amendment can be found in the specification at least, for example, on page 12, lines 12-19. Claims 32, 37, 38, 40 and 57 are amended for consistency.

Support for new claim 62 can be found in the specification at least, for example, on page 28, line 4.

Applicants submit that the amendments to claims introduce no new matter.

Declaration of Dr. Hans Deckmyn under 37 C.F.R. § 1.132

In support of Applicants' remarks in this response and as a submission of evidence in the present application, Applicants submit concurrently herewith a Declaration of Dr. Hans Deckmyn under 37 C.F.R. § 1.132 ("the Declaration"). As indicated at least in paragraphs 1 and 2 of the Declaration and the documents cited therein, Dr. Deckmyn is a recognized expert in the field of von Willebrand's disease and a co-inventor of the present application. Accordingly, Applicants respectfully request that the Examiner consider and give weight to the statements of fact, reasoning and observations of Dr. Deckmyn in the Declaration.

Rejections Under 35 U.S.C. § 103(a)

The Examiner maintained the claim rejections under 35 U.S.C. § 103(a) raised in the previous Office Action. Specifically, the Examiner maintained the rejections of claims 31, 40,

41, 48-50 and 60 under 35 U.S.C. § 103(a) as allegedly unpatentable over Favaloro in view of Christophe and Handin; claims 31-39, 41, 48-53 and 56-60 under 35 U.S.C. § 103(a) as allegedly unpatentable over Favaloro in view of Christophe, Hoylaerts and Handin; claim 54 under 35 U.S.C. § 103(a) as allegedly unpatentable over Favaloro in view of Christophe, Hoylaerts and Handin, and further in view of Batz; claim 55 under 35 U.S.C. § 103(a) as allegedly unpatentable over Favaloro in view of Christophe and Handin, and further in view of Solen; and claim 61 under 35 U.S.C. § 103(a) as allegedly unpatentable over Favaloro in view of Christophe, Hoylaerts and Handin, and further in view of Vincent. Applicants traverse the rejections for the reasons enumerated below.

The proper determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the claimed subject matter should be carried out and would have a reasonable likelihood of success. Both the suggestion and the expectation of success must be found in the prior art, not in Applicant's disclosure. *In re Dow Chemical Company*, 837 F.2d 469,473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fine*, 5 USPQ2d at 1600.

Applicants have amended claim 31 to further emphasize that the claimed invention is directed to a method for detecting von Willebrand's disease by, *inter alia*, detecting a binding activity of vWF in a sample to a soluble form or a portion of GP1b(α) that is not associated with a platelet in the presence of ristocetin or a functionally equivalent substance. Therefore, the claimed invention uses a soluble fragment of GP1b(α) to detect von Willebrand's disease based on its binding activity to vWF in a sample.

Based on the arguments presented in the response filed on July 31, 2006, and for the reasons set forth below, Applicants respectfully submit that the claimed invention is unobvious in view of the cited references because (1) there is no motivation to combine the teachings of primary reference with those of the secondary references and (2) that the prior art would not have suggested to one of ordinary skill in the art that the claimed invention should be carried out and would have a reasonable likelihood of success.

Motivation to combine

The Examiner acknowledges that the primary reference Favaloro teaches a collagen-binding assay (CBA) for measuring vWF activity in a method for detecting von Willebrand's disease and the secondary references teach ristocetin cofactor based assays. In maintaining the obviousness rejections, the Examiner however asserts that the CBA and the ristocetin cofactor assay were art-recognized equivalents at the time of the invention in a method for measuring vWF activity where it is immaterial whether the CBA or ristocetin cofactor is employed. Therefore, according to the Examiner, one of ordinary skill in the art would have found it obvious to substitute the CBA method for ristocetin cofactor assay. See, the Office Action, page 17, lines 15-19.

Applicants respectfully disagree with the Examiner. By contrast, Applicants submit that the CBA and the ristocetin cofactor assay were not art-recognized equivalents at the time the present application was filed (1999) for measuring vWF activity and that employing the CBA or ristocetin cofactor assay materially affects the diagnostic result of von Willebrand's disease. Applicants submit as evidence the Declaration executed by Dr. Deckmyn, a recognized expert in the field of von Willebrand's disease, to support Applicants' position. As set forth in paragraphs 4, Dr. Deckmyn states that, at the time the present application was filed (1999), it was known in the art that von Willebrand's disease is caused by defects or deficiencies in vWF, which is a large multimeric protein that possess multiple functions and activities essential to hemostasis. It was also known in 1999 that von Willebrand's disease is a heterogeneous disorder. "Sometimes, it is caused by the absence of the larger multimers also known as high molecular weight (HMW) vWF multimers. Sometimes, it is caused by the reduction or absence of all forms of vWF multimers. On other occasions, it is caused by mutations on the vWF protein that affect its specific functions. Depending on the nature of the defects or deficiencies, von Willebrand's disease can be classified into three major categories, namely, types 1, 2 and 3. Type 2 von Willebrand's disease can be further divided into subtypes 2A, 2B, 2M and 2N." See, the Declaration, paragraph 5. Dr. Deckmyn further states, in paragraph 6 of the Declaration, "[B]ecause of the heterogeneous nature of von Willebrand's disease, no single assay is robust enough to permit detection of all von Willebrand's disease types and subtypes in a patient. Due

to limitations of each assay, a test panel is therefore required to pinpoint specific defects entailed on vWF."

According to Dr. Deckmyn, at the time the present application was filed (1999), a number of diagnostic assays were known which detect different properties of vWF, among which were the CBA and the ristocetin cofactor assay (see, the Declaration, paragraph 7). In paragraph 7a of the Declaration, Dr. Deckmyn states the following:

> The CBA method measures the ability of vWF to bind to collagen, *i.e.*, the collagen-binding activity. The ristocetin cofactor assay, on the other hand, measures a specific vWF activity, *i.e.*, the ability of vWF to bind to the GP1b complex present on the surface of platelets in the presence of ristocetin or botrocetin (*i.e.*, the platelet GP1b-binding activity), which reflects the platelet adhesion and/or aggregation function of vWF in plasma. Therefore, the CBA and the ristocetin cofactor assay measures clearly distinct vWF activities associated with distinct biochemical functions.

Furthermore, Dr. Deckmyn states in paragraph 7b of the Declaration:

> At the molecular level, it was known in 1999 that the collagen-binding activity of vWF primarily involves the functional domain A3 of mature vWF. The platelet GP1b-binding activity of vWF primarily involves the functional domain A1.

Therefore, based on the statements of Dr. Deckmyn in the Declaration, Applicants submit that the CBA and the ristocetin cofactor assay measures clearly different vWF activities associated with distinct biochemical functions and molecular basis.

Furthermore, Dr. Deckmyn points out that it was known at the time that the present application was filed that the CBA method and the ristocetin cofactor assay use different laboratory procedures that provide different informations on vWF present in plasma. In paragraph 7c of the Declaration, Dr. Deckmyn states: "Procedurally, the CBA method uses ELISA test to measure the collagen-binding activity of vWF using immobilized collagen. The assay was developed based on collagen's selective ability to primarily recognize HMW vWF multimers. The CBA method, however, detects only some 30% of total vWF present in plasma. As a result, the CBA method provides very good information on the HMW multimers of vWF present, but does not provide a good estimate of total level of vWF. The ristocetin cofactor assay, on the other hand, uses ristocetin-induced platelet aggregation or agglutination procedure

to measure the platelet GP1b-binding activity of vWF. The ristocetin cofactor assay provides an estimate of the total level of vWF present and additional information on the quality of vWF present related to the size of multimers and specific functional defects." Thus, Dr. Deckmyn states that "whereas both the CBA method and the ristocetin cofactor assay are capable of detecting patients with subtypes 2A and 2B von Willebrand's disease due to the absence of HMW vWF multimers in the patients' plasma, only the ristocetin cofactor assay is sensitive in detecting patients with subtype 2M due to functionally defective vWF unrelated to a loss of HMW vWF forms."

Accordingly, Dr. Deckmyn concludes in paragraph 8 of the Declaration, that the CBA method and the ristocetin cofactor assay were not art-recognized equivalents at the time of the invention for measuring vWF activity and that employing the CBA or the ristocetin cofactor assay materially affects the diagnostic result in detecting von Willebrand's disease.

Applicants submit that the teachings in the primary reference, Favaloro, cited by the examiner further support that the CBA method and the ristocetin cofactor assay were not art-recognized equivalents and that employing the CBA or the ristocetin cofactor assay materially affects the diagnostic result in detecting von Willebrand's disease. Favaloro teaches that certain subtype 2B (*i.e.*, subtype IIB) patient plasma samples yielded normal or borderline ristocetin cofactor assay results, but gave clearly low CBA values (see, Favaloro, page 156, left column). In another word, according to Favaloro, the CBA method is more sensitive than the ristocetin cofactor assay in detecting subtype 2B von Willebrand's disease. Favaloro further states, if the ristocetin cofactor assay was employed, those subtype 2B patients could potentially be missed (see, Favaloro, page 157, left column). Thus, Favaloro demonstrates that employing the CBA or the ristocetin cofactor assay materially affects the diagnosis of von Willebrand's disease. Therefore, contrary to the Examiner's assertion, Applicants submit that one of ordinary skill in the art would not have found it obvious to substitute the CBA with the ristocetin cofactor assay because such a substitution would materially affect the diagnosis of von Willebrand's disease as taught in Favaloro and as known in the art at the time the present application was filed.

Furthermore, since Favaloro clearly teaches that the CBA method is more sensitive, therefore, a better method for detecting von Willebrand's disease than the ristocetin cofactor assay, Applicants submit that one of skill in the art contemplating improvements to the Favaloro

method would not have been motivated to substitute the CBA method with a ristocetin cofactor assay as taught in the secondary references.

Reasonable likelihood of success

Applicants submit that none of the cited references would have suggested to one of ordinary skill in the art that the claimed invention should be carried out and would have a reasonable likelihood of success. In raising the obviousness rejection, the Examiner states that Handin teaches a soluble fragment, glycocalicin, which contains the majority of the extracellular portion of GP1b(α), can inhibit ristocetin-dependent binding of vWF. The Examiner further states that Handin teaches a platelet aggregation assay for measuring vWF activity using ristocetin and recombinant (soluble) GP1b(α) containing vWF interaction site. Therefore, according to the Examiner, one of ordinary skill in the art would readily recognize that the use of Handin's soluble form of GP1b(α) would be advantageous in the platelet aggregation assay to detect specific GP1b-vWF binding activity (see, the Office Action, page 5, line 20, to page 6, line 12).

Applicants disagree with Examiner's characterization of the teachings of Handin. Handin teaches that soluble fragments such as glycocalicin or rGp1bαQ221-L318 can inhibit the ristocetin-dependent binding of vWF to platelets and Handin teaches an assay to demonstrate such inhibition ability of glycocalicin or rGp1bαQ221-L318. For example, as set forth in column 15, line 52, to column 16, line 3, Handin teaches: "The ability of recombinant GP1bα (rGP1bα) to inhibit ristocetin-dependent binding of [^{125}I]-vWF to platelets was assessed with paraformaldehyde-fixed platelets. . . . The ability of purified [glycocalicin] or the rGP1bα polypeptides to block vWF binding was assessed by adding increasing concentrations of the appropriate test substance to the assay mixture." Therefore, contrary to the Examiner's assertion, Handin teaches a platelet aggregation assay that uses a soluble fragment of GP1b(α) such as glycocalicin or rGp1bαQ221-L318 to measure its ability to inhibit vWF binding to platelets, not to measure the binding of vWF in a sample to the soluble fragment of GP1b(α) that is not associated with a platelet. In fact, Handin does not teach any assay to detect the binding activity of vWF in a sample to a soluble fragment of GP1b(α). Handin also does not teach or suggest that a soluble fragment of GP1b(α) can be successfully used to detect von Willebrand's disease.

Similarly, none of the other references cited by the Examiner teach or suggest that a soluble fragment of GP1b(α) can be successfully used to detect von Willebrand's disease based on its binding activity to vWF in a sample. As discussed previously, Favaloro teaches a method for detecting von Willebrand's disease using a collagen-binding assay. Christophe teaches a ristocetin induced platelet aggregation assay to characterize different properties of plasma vWF from normal individuals and from patients with type 2A and type 2B von Willebrand's disease (*see, e.g.*, Christophe, abstract and page 3554, left column and right column). Hoylaerts teaches use of an ELISA method to study how ristocetin mediates the binding of vWF to the GP1b complex (*see, e.g.*, Hoylaerts, page 454, left column, first paragraph). Batz teaches use of hydrophilic latex particles as carrier materials for biological and/or immunologically active substances in diagnostic agents (*see, e.g.*, Batz, abstract and the first paragraph in detailed description). Solen teaches a system and a method for measuring the platelet aggregation in whole blood in response to standard aggregating agents (*see, e.g.*, Solen, abstract). Vicente teaches a 45 KDa GP1b(α) N-terminal fragment of GP1b(α) (glycocalicin) that is capable of interacting with purified surface-bound vWF (*see, e.g.*, Vicente, abstract, page 18475, left column). Therefore, not one of the cited references teach or suggest that a soluble fragment of GP1b(α) can be successfully used to detect von Willebrand's disease based on its binding activity to vWF in a sample.

Whether a soluble fragment of GP1b(α) can be successfully used to detect von Willebrand's disease based on its binding to vWF in a plasma sample depends on whether such a binding activity would be robust enough to provide clinically relevant test data to allow accurate discrimination between normal samples and samples from patients with von Willebrand's diseases. One of the references cited by the Examiner, Christophe, attempted to address this question. Christophe compared the binding capacity of plasma vWF from type 2 (*i.e.*, type II) von Willebrand's disease patients and normal controls to a soluble fragment of GP1b(α) glycocalicin and to platelet GP1b (see, Christophe, page 3554, left column). Christophe found that, while ristocetin-induced binding of plasma vWF to fixed platelets correlated with the clinical phenotypes of type 2 von Willebrand's disease, the binding of plasma vWF from type 2 von Willebrand's disease patients to glycocalicin is normal (see, Christophe, Figure 6, Table 1 and page 3557, right column and page 3560, left column). In other words, Christophe disclosed

that the binding activity between vWF in a plasma sample and a soluble fragment of GP1b(α) glycocalicin detected in its experiment did not provide clinically relevant data to allow discrimination between normal samples and samples from patients with von Willebrand's diseases. Therefore, one of skill in the art in view of the teachings in Christophe would have been discouraged to use a soluble fragment of GP1b(α) instead of platelets to detect von Willebrand's disease. One of skill in the art in view of the teachings in Christophe also would not have expected that a soluble fragment of GP1b(α) can be successfully used to detect von Willebrand's disease based on its binding activity to vWF in a sample.

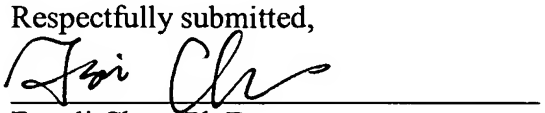
Indeed, despite the fact that it had been known since 1988 that a soluble fragment of GP1b(α) glycocalicin is capable of binding to vWF, no one had successfully used glycocalicin or any other soluble fragment of GP1b(α) to detect von Willebrand's disease based on the binding activity between the vWF and the soluble fragment of GP1b(α) prior to Applicants' invention. Applicants discovered for the first time that such a soluble fragment can be successfully used to detect von Willebrand's disease using the method described and claimed in the present application. Therefore, Applicants invented a method for detecting von Willebrand's disease using a soluble fragment of GP1b(α), which the prior art had not suggested should be carried out or would have a reasonable likelihood of success.

Applicants therefore respectfully submit that claim 31 and any claims dependent therefrom are novel and unobvious over Favaloro, Christophe, Handin, Hoylaerts, Batz, Solen, and Vincent because (1) there is no motivation to combine the teachings of primary reference Favaloro with those of the secondary references and (2) that the teachings of the cited references would not have suggested to one of ordinary skill in the art that the claimed subject matter would have a reasonable likelihood of success. Applicants therefore respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a).

CONCLUSION

Applicants believe that all of the art of record has been overcome and claims 31-41 and 46-62 are in condition for allowance. The Examiner is invited to telephone the undersigned attorney to discuss any remaining issues. Early and favorable actions are respectfully solicited.

Respectfully submitted,



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